

## **Evidence Report**

# Chapter 1. Introduction

The Social Security Administration (SSA) of the Department of Health and Human Services requested that the Agency for Healthcare Research and Quality (AHRQ), through its Evidence-based Practice Center (EPC) program, produce an evidence report to determine whether specific factors or combination of factors alone or in addition to birth weight predict significant developmental disability in former premature infants and whether premature infants with such factors have long-term developmental disabilities. This is one of three reports requested by SSA in the broader topic of “Criteria for Determining Disability in Infants and Children.” The evidence reports are prepared to assist the SSA in updating its *Listing of Impairments*, and revising its disability policy, as may be appropriate.

## Definition of Disability

The definition of disability in children used for the purposes of this report came from the SSA and was based on a definition passed by Congress in 1996. Under Title XVI, a child under age 18 years will be considered disabled if he or she has a medically determinable physical or mental impairment or combination of impairments that causes marked and severe functional limitations, and that can be expected to cause death or that has lasted or can be expected to last for a continuous period of not less than 12 months.

Specific areas of functioning include: 1) acquiring and using information, 2) attending and completing tasks, 3) interacting and relating with others, 4) moving about and manipulating objects, 5) caring for yourself, 6) health and physical well-being. Disability is based on the degree to which the above functions are interfered with. Disability is established, if there are marked limitations in at least two areas or there is an extreme limitation in one area of functioning. Where standardized tests of function exist, the regulations define a “marked” degree of functional limitation as more than two but less than three standard deviations below the mean and an “extreme” limitation as three or more standard deviations below the mean. This definition is an administrative definition and is not always applicable to evidence available in the literature since disability as strictly and narrowly defined by US Congress and interpreted by the SSA is not the intent of the studies available in the literature. Although there is no single, standardized definition of disability, the literature provides overwhelming relevant evidence of functional impairments, disabilities, and limitations of VLBW.

## Definition of Prematurity

Prematurity is defined both by gestational age and by birth weight criteria. The World Health Organization (WHO) defines prematurity as less than 37 weeks gestation. Birth weight has been and continues to be used as a surrogate definition of prematurity because birth weight and gestational age are closely correlated and birth weight data are readily available. Also, there is variable reliability of gestational age assessment in specific datasets. Defining specific gestational age or birth weight ranges often further refines the degree of prematurity.

The lower the gestational age, the more immature is an infant. Generally, the lower the birth weight, the more immature is an infant. However, birth weight is not a perfect measure of immaturity since infants may have birth weights that are disproportionate with their gestational age. For instance, some infants may be small or large for their gestational age.

Studies frequently focus on specific birth weight or gestational age groups. VLBW infants (birth weight less than 1500 grams) belong to one common birth weight category that targets infants at increased risk for problems associated with prematurity. This category of VLBW is often divided into subcategories of lower birth weights (less than 1250, less than 1000, less than 750 grams) to facilitate analyses of infants within different birth weight strata.

Similarly, gestational age categories of premature infants often include groupings of premature infants less than 28 weeks gestation, 28 to 32 weeks gestation, 32 to 36 weeks gestation, or less than 36 weeks gestation. Gestational age criteria, less than 32 weeks gestational age is considered by some authorities as “very premature” and less than 28 weeks gestational age as “extremely premature.”

## The Problem of Prematurity

Premature birth is an important public health problem due to the number of births in this category each year, the serious complications of prematurity, and the life-long tangible and intangible costs of caring for these infants. Among the 4,058,814 births in the USA in 2000, 58,124 (1.43%) were VLBW (less than or equal to 1500 grams) and 467,201 (11.6%) were born preterm as defined as less than 37 weeks gestational age (Table A).

**Table A. Live birth distribution organized by birth weight and gestation in the United States in the year 2000 (National Vital Statistics Reports, 2000).**

Birth weight grams	Number	Percent	Gestation weeks	Number	Percent
Total live births	4,058,814	100	Total live births	4,058,814	100
< 500 gm	5,952	0.15	<23 wk	9,243	0.2
500 – 750 gm	11,032	0.27	24-28 wk	19,652	0.5
751-1000 gm	11,878	0.29	28-31 wk	48,624	1.2
1001-1250 gm	13,291	0.33	32-35	218,928	5.5
1251-1500 gm	15,971	0.39	36-37	497,220	12.4
>1501 gm	3,995,849	98.57	38-47 wk	3,221,809	80.2
Not stated	4,841		Unknown	43,338	

Although VLBW is a relatively small proportion (1.4%) of total births in the US, this category of infants accounts for the highest neonatal mortality and morbidity among newborns, as well as significant tangible and intangible lifelong costs to the family and society for medical care, and ancillary health and educational services.

Advances in neonatal/perinatal medicine have improved the survival and the quality of survival of premature infants. Ninety-six percent of infants with birth weights between 1251 and 1500 grams survive in contrast to 77% of infants with birth weight less than 1250 grams (Stevenson, Wright, Lemons, et al., 1998). Despite these advances, infants born prematurely experience a disruption in the normal process of growth and development. The degree of disruption in the growth and development of each organ system, and the subsequent disabilities, are inversely proportional to gestational age at birth. For any adverse sequelae associated with premature birth, the incidence and the severity of the complication is inversely proportional to the gestational age [Table B]. For instance, 12% of infants with birth weight between 1251 grams and 1500 grams survived with at least one major, acute morbidity in contrast 53% with birth weight 501-1250 grams (Stevenson, Wright, Lemons, et al., 1998).

**Table B: Mortality and morbidity of premature infants by birth weight born in NICHD Neonatal Research Network between January 1, 1993 and December 31, 1994 (Stevenson, Wright, Lemons, et al., 1998).**

Complication	Birth Weight 501-1250 grams	Birth Weight 1251-1500 grams
N	3176	1417
Mortality (%)	23	4
Severe ICH* (Grade 3-4) (%)	16	3
Periventricular leukomalacia (%)	7	4
NCLD** at 36 wk PMA***	24	8
Necrotizing enterocolitis	9	3

\* ICH = intracranial hemorrhage

\*\* NCLD = neonatal chronic lung disease

\*\*\* PMA = postmenstrual age (gestational age + chronological age in weeks = adjusted gestational age)

## Factors Associated with Disability in VLBW Infants

Surviving premature infants often sustain multi-organ system complications that may persist beyond the first few years of life and frequently result in permanent disabilities. Examples include major neurodevelopmental impairments, such as cerebral palsy (CP), mental retardation (MR), deafness and disorders of speech/language/communication, perception, attention, behavior and learning disorders, blindness or other visual disabilities, chronic lung disease, and growth retardation.

Complications of even a single organ system may have a profound impact upon other organ systems. A classic example of this is BPD, a neonatal chronic lung disease, which still occurs in 50% of extremely low birth weight (ELBW is defined as birth weight less than 1 kg) survivors (Stevenson, Wright, Lemons, et al., 1998). In addition to pulmonary disability, BPD predisposes infants to cardiovascular and neurodevelopmental disabilities, abnormal growth (height and weight), increased unfavorable ophthalmic risk, and more frequent infections (Farrell and Fiascone, 1997; Bancalari, 1997). Other determinants of disability of prematurity are summarized below. As previously noted, biomedical determinants of disability in premature infants are often compounded by determinants of social and psychological adaptation of these vulnerable children and their families.

CNS complications of prematurity, such as cerebral white matter damage, intraventricular hemorrhage, hypoxic-ischemic encephalopathy, and infection (e.g. meningoencephalitis), are related to both the degree of prematurity and illness acuity. CNS complications of prematurity are associated with life-long neurodevelopmental disabilities that may adversely impact an infant's cognitive, motor, visual, auditory, and psychosocial-behavioral development. Visual and audiologic compromises are individually important factors and have enormous impact on the overall cognitive, motor, and psychosocial development of premature babies (Hack and Fanaroff, 1999; Piesuch, Leonard, Cooper, et al., 1997; Kuban, Sanocka, Leviton, et al., 1999; Perlman, 1998; Stewart, Reynolds, Hope, et al., 1987; Stewart, Reynolds, Hope, et al., 1993). CNS complications of prematurity are associated with mental retardation and CP in premature infants.

ROP is an abnormal retinal vascular development. Severe ROP remains a leading cause of permanent vision compromise and blindness in premature infants (Murphy and Good, 1997; Oxford Registry of Vision Impairment, 1995). Although current retinal ablative therapy has helped reduce the incidence of retinal detachment and blindness, fewer than 20% of 5½-year-old children who developed threshold (severe) ROP and were treated achieved 20/40 vision (Cryotherapy for Retinopathy of Prematurity Group, 1996).

BPD is a chronic disease of the lung that affects almost exclusively premature infants. BPD is associated with increased mortality and morbidity both short-term and long-term. The multi-system morbidity of BPD may be associated with compromised cardiopulmonary function, growth, and neurosensory development.

Gastrointestinal complications (e.g. necrotizing enterocolitis and short-gut syndrome) (Stoll and Kliegman, 1994) and nutritional complications of prematurity (e.g. inadequate nutritional and nutrient intake related to prematurity, chronic hepatic injury secondary to prolonged total parenteral nutrition, and osteomalacia which compromises bone growth) may adversely impact life-long growth potential, and nutritional tolerance (Hay, Lucas, Heird, et al., 1999). Intrauterine circumstances and postnatal nutrition may program premature infants for life-long disorders (Lucas, 1990; Seckl, 1998).

The immune system of premature infants is also disrupted in its normal growth and development (Yoder and Polin, 1997). Premature infants are at increased risk for serious infections well beyond the neonatal hospitalization. The immune response to immunizations of infants who were born prematurely is less than that of infants who were born full term. The morbidity and mortality related to increased risk of infection among infants born prematurely may persist for years (Read, Clemens, and Klebanoff, 1994).

Inadequate growth in terms of both length and weight is a well-recognized, frequent, and persistent long-term complication of prematurity (Ehrenkranz, 2000; Doyle, 2000; Hack, 1996). Compromised growth among former premature infants may be due to multiple biomedical determinants including pulmonary, gastrointestinal, endocrine, neurological, and nutritional complications. Often the medical reasons for compromised growth in children born prematurely are compounded by familial, psychosocial, and socioeconomic factors, which independently compromise normal growth and development.

Educational achievement, self-esteem, psychosocial development, and effective integration into society are of particular concern as greater numbers of very premature infants are surviving in a society where resources for effective educational and psychosocial intervention are increasingly scarce and difficult to access. Former premature infants have increased incidence of learning disabilities and increased need for special education (Hack, Taylor, Klein, et al., 1994, Msall and Tremont, 2000). Obviously educational, emotional, and social successes, or the lack

thereof, for former premature infants have a major impact on how these individuals ultimately function as adults and upon the fabric of our society as a whole (Park and Hogan, 2000; Lester and Miller-Loncar, 2000; Saigal, 2000).

Thus numerous biomedical as well as familial, socioeconomic, and psychosocial factors related to prematurity predict disability in former premature infants. Unfortunately, many premature infants, especially the most immature infants, often experience a combination of factors, which further compound the magnitude and complexity of their life-long disabilities. Acute and long-term complications of premature infants, coupled with a family's ability to provide and advocate for their premature infants, have a substantial impact on the individual patient, their family, and society beyond the utilization of health care resources.

A systematic review of the incidence, types, and severity of factors, and the combination of factors, which predict long-term disabilities of premature infants, is worthwhile considering the societal impact of increasing number of surviving former premature infants. Review of recent literature may shed insights on whether factors related to premature birth predict future disability.

This review will summarize evidence on VLBW infants (i.e. prematurity) with or without other conditions to determine whether VLBW is associated with long-term disabling outcomes. The primary outcomes of interest included in this review are cerebral palsy, mental retardation, hearing/speech/language/and behavioral disability, visual disability, adverse pulmonary function, and disrupted growth.